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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,721	REISNER, YAIR	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, 5, 7, 9- 14, 16-17,19-21 and 19-69* is/are pending in the application.

4a) Of the above claim(s) *22-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 7, 9- 14, 16-17,19-21 and 46-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 03/22/04 is acknowledged.

Claims 1, 2, 5, 7, 9- 14, 16-17 and 19-69 are pending.

Claims 22-45 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1, 2, 5, 7, 9- 14, 16-17, 19-21 and 46-69, drawn to a method of inducing tolerance to transplant and method of transplanting a transplant, comprising a step of administering to the recipient a dose of tolerance-inducing cells are under consideration in the instant application.

In view of the amendment, filed 03/22/04 , the following rejection remains:

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

3. Claims 1, 2, 5, 7, 9- 14, 16-17, 19-21 and 46-55, 58- 66 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,806,529 in view of Bachar-Lustig E et al. (Blood, 1999, v 94, pp 3212-3221) , or Mobest D et al. (Biotechnology and Bioengineering, 1998, v. 60 pp. 341-347), or Vavrova et al. (Hematol.Cell Ther. 1999, v.41 pp105-112) for the same reasons set forth in the previous Office Action, mailed 12/29/03.

Applicant's arguments, filed 03/22/04 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) Bachar-Lustig E et al ., teaches that it is not possible to culture CD34+ cells for expansion of veto cells; (ii) Sca1+ Lin- mouse cells are composed of both $Cd34^{+}$ and $CD34^{-}$ cells which is clearly non-homologous to the purified human CD34+ cells taught by the instant invention; (iii) newly submitted claims 49 and 60 each including limitation of the donor or recipient is a human; (iv) the growth condition taught by the instant specification involve a culture medium containing FCS, FLT-3-ligand, SCF and TPO; (v) the growth conditions taught

by Vavrova et al. and Mobest at al., are different from the conditions taught by the present specification since growth condition taught by Vavrova et al. and Mobest at al will generate about 11% of CD33+CD34+ cells that is in sharp contrast with 33% of the Cd33+Cd34+ cells obtained according to the teaching of the present invention.

Applicant is respectfully reminded that the rejection under 35 USC103 does not set any specific time frame when the attempts to combine the references should be made.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

It is noted that the amended claims now recited culturing HPC population derived from a donor wherein the donor is allogeneic or xenogeneic and wherein the recipient and/or donor is a human.

However, the '529 Patent teaches a method of inducing tolerance to a transplant during bone marrow transplantation comprising administering HPC cells derived from allogenic donor (see entire document, Abstract in particular) . The '529 Patent also teaches that host patient is conditioned prior to the transplantation of hematopoietic stem cells (HPC) . Conditioning may be carried out under sublethal, lethal or supralethal conditions (see column 3, lines 51-60 in particular). The '529 Patent also teaches that donor and recipient are both humans (see Example 1 in particular). The '529 Patent also teaches that said method enable engraftment of MHC-mismatched transplants (see column 2, lines 36-42 in particular).

The '529 Patent does not teaches that said HPC cells, derived from the donor are *ex vivo* culturing under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant.

It appears that Applicant and the Examiner differ on the interpretation of the prior art. It is the Examiner position that Bachar-Lustig E. et al. teach that it is possible to culture HPC cells under growth conditions, suitable for inducing or enhancing tolerance-inducing activity of CD34+ cells by expanding *in vitro* the CD34+ cells and use them for transplantation (see entire document, abstract and page 3220 in particular). Applicant's attention is drawn to left column on page 3220, wherein Bachar-Lustig et al., explicitly teaches that " it may be possible to expand in vitro the CD34+ cells possessing veto activity and use them together with a small number of pluripotential cells for transplantation."

With regards to Applicant's comments that Sca1+ Lin- mouse cells are composed of both $Cd34^{+}$ and $CD34^{-}$ cells which is clearly non-homologous. It is noted that the amended claimed recites cultured HPC population, not purified CD34+ cells. Moreover, Claim 51 clearly recited that CD34+ cells make up at least 48.6 % of cultured HPC population. Clearly, one skilled in the art at the time the invention was made would not consider a cell population comprising up to 48.6 % of $CD34^{+}$ cells to be purified , homologous population of only CD34+ cells.

With regards to Applicant's comments that the growth condition taught by the instant specification involve a culture medium containing FCS, FLT-3-ligand, SCF and TPO; and the growth conditions taught by Vavrova et al. and Mobest at al., are different from the conditions taught by the present specification. It is noted that growth medium containing FCS, FLT-3-ligand, SCF and TPO for ex-vitro expansion of Cd34+ cells was well known in the art at the time the invention was made. Applicant himself acknowledge that fact by referenced to Qie et al. (see page 49 of the specification as filed). Moreover, in Applicant's Response filed on March 20, 2003 Applicant also acknowledge that " the prior art cited by te examiner describes culturing methods with which expansion of HPC can be effected". (see page 5 in particular). In addition it is noted that culture medium containing FCS, FLT-3-ligand, SCF and TPO is not claimed in the instant claims. It is the examiner position that it would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

With regards to Applicant's comments that growth condition taught by Vavrova et al., and Mobest at al., will generate about 11% of CD33+CD34+ cells that is in sharp contrast with 33% of the Cd33+Cd34+ cells obtained according to the teaching of the present invention. It is noted that the current claims are not drawn to the improved method for obtaining the enriched population of CD33+CD34+ cells. Applicant himself acknowledge that the prior art method of expansion of HPC cells will result in generation of Cd33+Cd34+ . Clearly, it would be conventional and within the skill of the art to identify the optimum culturing conditions suitable for inducing myeloid differentiation of cultured HPSc. In addition, Mobest et al. teach the methodology of analyzing the role of individual components of culturing medium for inducing myeloid differentiation of cultured HPSc (see page 344 in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the

optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Mobest et al., teach *ex vivo* expansion of human CD34+ hematopoietic progenitor cells under condition suitable for inducing differentiation of said cells into $CD33^+$ myeloid phenotype cells (see entire document, Abstract in particular). Mobest et al., also teach that successful ex vivo culture and amplification of human CD34+ hematopoietic progenitor cells that would differntiate into $CD33^+$ myeloid phenotype cells offers the possibility of additional graft manipulation steps, e.g. depletion or elimination of contaminating tumor cells in Autologous grafts, amplification of bone marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells (see page 341 in particular). The growth condition taught by Mobest et al. are the same as to growth conditions disclosed in the instant specification (see Materials and Method in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Vavrova et al. teach a method of *ex vivo* expansion and differentiation of human HPC cells under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells (see entire document, Abstract and page 106 in particular). Vavrova et al., teach that *ex vivo* expansion of HPC would benefit studies including accelerated engraftment, reduced risk of infection, smaller stem cell harvest and improved effectiveness of genetically modified stem cells. The growth condition taught by Vavrova et al. are the same as to growth conditions disclosed in the instant specification (see Materials and Method and Table 3 in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., to those of The '529 Patent, to obtain a claimed method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipiet comprising a step of *ex vivo* culturing HPC, derived from the donor under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because successful *ex vivo* culture and amplification of human CD34+ hematopoietic progenitor cells under growth conditions that would stimulated to differentiation of the said cells into $CD33^{+}$ myeloid phenotype cells prior to transplantation of the transplant offers additional possibility and would be beneficial in accelerated engraftment, reduced risk of infection, additional graft manipulation steps, e.g. depletion or elimination of contaminating tumor cells in autologous grafts, amplification of bone marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells as taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al. These *ex vivo* cultured , amplified and differentiated CD34+ hematopoietic progenitor cells can be further used in a method of inducing tolerance to a transplant during bone marrow transplantation taught by the '529 Patent. Since the growth condition taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., are the same as to growth conditions disclosed in the instant specification it would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Claims 46 , 47 58 and 69 are included because it would be conventional and within the skill of the art to identify the optimum culturing conditions suitable for inducing myeloid differentiation of cultured HPSc. In addition, Mobest et al. teach the methodology of analyzing the role of individual components of culturing medium for inducing myeloid differentiation of cultured HPSc (see page 344 in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 50-55 and 61-66 are included because the claimed functional limitation would be an obvious properties of the known and referenced method of *ex-vitro* culturing of HPS. because that both the prior art and applicant administer the same method of *ex-vitro* culturing of HPS. When the prior art method is the same as a method described in the specification, it can be assumed the method will obviously perform the claimed process absent a showing of unobvious property.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The following new grounds of rejection are necessitated by the amendment filed 03/22/04

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 49 , 56, 57, 58, 60, 67, 68 and 69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

"... wherein said HPC population derived from the donor is a population of substantially purified CD34+ cells", claimed in claims 49 and 60; " wherein the transplant is substantially of non-hematopoietic origin" claimed in claims 56 and 67; "wherein the donor is not myelosuppressed or is not is not potentially myelosuppressed" claimed in claims 57 and 68 and " whereas said growth conditions do not include supplementation with IL-1 beta, IL-3, IL-6 and/or IL-11" claimed in claims 58 and 69 represent a departure from the specification and the claims as originally filed. The passages pointed by the applicant do not provide a clear support for "... wherein said HPC population derived from the donor is a population of substantially purified CD34+ cells", claimed in claims 49 and 60; " wherein the transplant is substantially of non-hematopoietic origin" claimed in claims 56 and 67; "wherein the donor is not myelosuppressed or is not is not potentially myelosuppressed" claimed in claims 57 and 68 and " whereas said growth conditions do not include supplementation with IL-1 beta, IL-3, IL-6 and/or IL-11" claimed in claims 58 and 69.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 56 , 57 , 67 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,806,529 in view of Bachar-Lustig E et al. (Blood, 1999, v 94, pp 3212-3221) , or Mobest D et al. (Biotechnology and Bioengineering, 1998, v. 60 pp. 341-347), or Vavrova et al. (Hematol.Cell Ther. 1999, v.41 pp105-112) as applied to claims 1, 2, 5, 7, 9- 14, 16-17, 19-21 and 46-55, 58- 66 , and 69 above, and further in view of US Patent 6,558662.

The teaching of US Patent 5,806,529 , Bachar-Lustig E et al., Mobest D et al. and Vavrova et al. have been discussed, supra.

The claimed invention differs from the reference teaching in that the combined references do not teach that transplant is substantially non-hematopoietic original, as claimed in claims 56 and 67 or wherein the donor is not myelosuppressed.

US Patent '662 teaches a a successful method of treating GVHD during transplant transplanted from a donor to a recipient, wherein transplant is non-hematopoietic original and wherein donor is not myelosuppsesed recipient, comprising culturing an donor stem cell *ex vivo* for transplantation (see entire document, Abstract and columns 3 and 17 in particular). US Patent '662 teaches that donor is not myelosuppsesed (see column 2 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching US Patent '662 to those of Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., and the '529 Patent, to obtain a claimed method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipient whrein transplant is substantially non-hematopoietic originaland wherein the donor is not myelosuppressed

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because US Patent '662 teaches a successful method of treating GVHD during transplant transplanted from a donor to a recipient, wherein transplant is non-hematopoietic original and wherein donor is not myelosuppsesed and wherein donor stem cells are expanded *ex vivo* for transplantation. Said *ex vivo* expanded cells can be cultured as taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al. These *ex vivo* cultured , amplified and differentiated CD34+ hematopoietic progenitor cells can be further used in a method of inducing tolerance to a transplant during bone marrow transplantation taught by the '529 Patent. Since the growth condition taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., are the same as to growth conditions disclosed in the instant specification it would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. It is noted that the Specification at page 48 disclosed a Table 1 comprising text in foreign language that is not appropriate for applications filed in US.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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